31-05-2000
Case number
PCT/GB99/00838
30 May 2000
CLMS
ART 34 AMDT

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## Claims

1.     An isolated mammalian sodium channel protein comprising
   (i)     The amino acid sequence shown in SEQ I.D No 2 or
   (ii)     A variant thereof which has at least 70% identity to the amino acid
   sequence of SEQ I.D. No 2.

2.     A protein according to claim 1 wherein the variant has at least 90% identity to
the amino acid sequence of SEQ I.D. No 2.

3.     An isolated sodium channel protein according to claim 1 ~~or 2~~ which is a
human protein.

4.     An isolated sodium channel protein according to claim 1 which is derivable
from the dorsal root ganglion of a mammal and which has an IC50 for TTX of
about 1 μM.

5.     An isolated nucleotide sequence encoding a sodium channel protein or
variant thereof according to ~~any one of claims 1 to 4~~ Claim 1.

6.     An isolated nucleotide sequence according to claim 5 which is a DNA
sequence.

7.     An isolated nucleotide  sequence according to claim 5 which comprises:
   (a)     the nucleic acid sequence of SEQ ID NO 1 and/or a sequence
   complementary thereto; or
   (b)     a sequence which hybridises under stringent conditions to a sequence
   as defined in (a); or
   (c)     a sequence that is degenerate as a result of the genetic code to a
   sequence as defined in (a) or (b); or
   (d)     a sequence having at least 70% identity to a sequence as defined in
   (a), (b) or (c).

8.     A recombinant polynucleotide which comprises:

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(a) one or more of the nucleotide sequences of SEQ ID NO 3 to 17 and/or a
sequence complementary thereto; or

(b) a sequence which hybridises under stringent conditions to a sequence as
defined in (a); or

5 (c) a sequence that is degenerate as a result of the genetic code to a
sequence as defined in (a) or (b); or

(d) a sequence having at least 70% identity to a sequence as defined in (a),
(b) or (c).

10 9. A recombinant polynucleotide according to claim 8 which comprises all of the
sequences as defined in SEQ ID 3 to 17 wherein ascending numerical order
represents the order in which the SEQ ID is read in the 5' to 3' direction

10. An isolated amino acid sequence encoded for by a nucleotide according to
15 claim 8 ~~or 9~~.

11. An expression vector comprising a polynucleotide according to ~~any one of~~ Claim 5 or
~~claims 5 to 9~~.

20 12. A host cell comprising an expression vector according to claim 11.

13. An antibody or fragment thereof which recognises and binds to a polypeptide
according ~~any one of claims 1 to 4~~ Claim 1.

25 14. An isolated polypeptide according to ~~any one of claims 1 to 4~~ Claim 1 for use in a
method of screening for agents with analgesic or anti-hypersensivity activity.

15. A method for the identification of a modulator of a sodium channel protein
according to ~~any one of claims 1 to 4~~ Claim 1, comprising contacting said protein with
30 a test compound and detecting changes in the activity of the sodium channel
protein due to the test compound.

16. A method of determining whether a test compound is a modulator of sodium
flux which method comprises expressing a protein according to ~~any one of~~ Claim 1

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_claims 1 - 4_ in a host cell; contacting said protein with a test compound; and measuring sodium flux.

17. A modulator identifiable by a method according to claim 15 ~~or 16~~, for use in therapy.

18. Use of a modulator indentifiable by a method as claimed in claim 15 ~~or 16~~ for the manufacture of an analgesic or anti-hypersensitivity medicament.

19. A method of treating a disorder which is responsive to modulation of a protein according to ~~any one of claims 1 to 4~~ claim 1 which method comprises administering to a patient an effective amount of a modulator, identifiable by a method according to claim 15 ~~or 16~~.

Team leader
Said. Keep Wit
CLM

1 GGAGCCATAC GGTGCCCTGA TCCTCTGTAC CAGGAAGACA GGGTGAAGAT

51 GGAGGAGAGG TACTACCCGG TGATCTTCCC GGACGAGCGG AATTTCCGCC

101 CCTTCACTTC CGACTCTCTG GCTGCCATAA AGAAGCGGAT TGCTATCCAA

151 AAGGAGAGGA AGAAGTCCAA AGACAAGGCG GCAGCTGAGC CCCAGCCTCG

201 GCCTCAGCTT GACCTAAAGG CCTCCAGGAA GTTACCTAAG CTTTATGGTG

251 ACATTCCCCC TGAGCTTGTT ACGAAACCTC TGGAGGACCT GGACCCCTAC

301 TACAAAGACC ATAAGACATT CATGGTGTTG AACAAGAAAA GAACAATTTA

351 TCGCTTCAGC GCCAAGCGGG CCTTGTTCAT CTGGGGCCT TTTAATCCCC

401 TCAGAAGCTT AATGATTCGT ATCTCTGTCC ATTCAGTCTT TAGCATGTTC

451 ATCATCTGCA CGGTGATCAT CAACTGTATG TTCATGGCGA ATTCTATGGA

501 GAGAAGTTTC GACAACGACA TTCCCGAATA CGTCTTCATT GGGATTTATA

551 TTTTAGAAGC TGTGATTAAA ATATTGGCAA GAGGCTTCAT TGTGGATGAG

601 TTTTCCTTCC TCCGAGATCC GTGGAACTGG CTGGACTTCA TTGTCATTGG

651 AACAGCGATC GCAACTTGTT TTCCGGGCAG CCAAGTCAAT CTTTCAGCTC

701 TTCGTACCTT CCGAGTGTTC AGAGCTCTGA AGGCGATTTC AGTTATCTCA

751 GGTCTGAAGG TCATCGTAGG TGCCCTGCTG CGCTCGGTGA AGAAGCTGGT

801 AGACGTGATG GTCCTCACTC TCTTCTGCCT CAGCATCTTT GCCCTGGTCG

851 GTCAGCAGCT GTTCATGGGA ATTCTGAACC AGAAGTGTAT TAAGCACAAC

901 TGTGGCCCCA ACCCTGCATC CAACAAGGAT TGCTTTGAAA AGGAAAAAGA

5    951 TAGCGAAGAC TTCATAATGT GTGGTACCTG GCTCGGCAGC AGACCCTGTC

1001 CCAATGGTTC TACGTGCGAT AAAACCACAT TGAACCCAGA CAATAATTAT

1051 ACAAAGTTTG ACAACTTTGG CTGGTCCTTT CTCGCCATGT CCGGGTTAT

10   1101 GACTCAAGAC TCCTGGGAGA GGCTTTACCG ACAGATCCTG CGGACCTCTG

1151 GGATCTACTT TGTCTTCTTC TTCGTGGTGG TCATCTTCCT GGGCTCCTTC

15   1201 TACCTGCTTA ACCTAACCCT GGCTGTTGTC ACCATGGCTT ATGAAGAACA

1251 GAACAGAAAT GTAGCTGCTG AGACAGAGGC CAAGGAGAAA ATGTTTCAGG

1301 AAGCCCAGCA GCTGTTAAGG GAGGAGAAGG AGGCTCTGGT TGCCATGGGA

20   1351 ATTGACAGAA GTTCCCTTAA TTCCCTTCAA GCTTCATCCT TTTCCCCGAA

1401 GAAGAGGAAG TTTTTCGGTA GTAAGACAAG AAAGTCCTTC TTTATGAGAG

25   1451 GGTCCAAGAC GGCCCAAGCC TCAGCGTCTG ATTCAGAGGA CGATGCCTCT

1501 AAAAATCCAC AGCTCCTTGA GCAGACCAAA CGACTGTCCC AGAACTTGCC

1551 AGTGGATCTC TTTGATGAGC ACGTGGACCC CCTCCACAGG CAGAGAGCGC

30   1601 TGAGCGCTGT CAGTATCTTA ACCATCACCA TACAGGAACA AGAAAAATTC

1651 CAGGAGCCTT GTTTCCCATG TGGGAAAAAT TTGGCCTCTA AGTACCTGGT

35   1701 GTGGGACTGT AGCCCTCAGT GGCTGTGCAT AAAGAAGGTC CTGCGGACCA

1751 TCATGACGGA TCCCTTTACT GAGCTGGCCA TCACCATCTG CATCATCATC

**SUBSTITUTE SHEET (RULE 26)**

1801 AATACCGTTT TCTTAGCCGT GGAGCACCAC AACATGGATG ACAACTTAAA

1851 GACCATACTG AAAATAGGAA ACTGGGTTTT CACGGGAATT TTCATAGCGG

5

1901 AAATGTGTCT CAAGATCATC GCGCTCGACC CTTACCACTA CTTCCGGCAC

1951 GGCTGGAATG TTTTTGACAG CATCGTGGCC CTCCTGAGTC TCGCTGATGT

10  2001 GCTCTACAAC ACACTGTCTG ATAACAATAG GTCTTTCTTG GCTTCCCTCA

2051 GAGTGCTGAG GGTCTTCAAG TTAGCCAAAT CCTGGCCCAC GTTAAACACT

2101 CTCATTAAGA TCATCGGCCA CTCCGTGGGC GCGCTTGGAA ACCTGACTGT

15  2151 GGTCCTGACT ATCGTGGTCT TCATCTTTTC TGTGGTGGGC ATGCGGCTCT

2201 TCGGCACCAA GTTTAACAAG ACCGCCTACG CCACCCAGGA GCGGCCCAGG

20  2251 CGGCGCTGGC ACATGGATAA TTTCTACCAC TCCTTCCTGG TGGTGTTCCG

2301 CATCCTCTGT GGGGAATGGA TCGAGAACAT GTGGGGCTGC ATGCAGGATA

2351 TGGACGGCTC CCCGTTGTGC ATCATTGTCT TTGTCCTGAT AATGGTGATC

25
    2401 GGGAAGCTTG TGGTGCTTAA CCTCTTCATT GCCTTGCTGC TCAATTCCTT

2451 CAGCAATGAG GAGAAGGATG GGAGCCTGGA AGGAGAGACC AGGAAAACCA

30  2501 AAGTGCAGCT AGCCCTGGAT CGGTTCCGCC GGGCCTTCTC CTTCATGCTG

2551 CACGCTCTTC AGAGTTTTTG TTGCAAGAAA TGCAGGAGGA AAAACTCGCC

2601 AAAGCCAAAA GAGACAACAG AAAGCTTTGC TGGTGAGAAT AAAGACTCAA

35
    2651 TCCTCCCGGA TGCGAGGCCC TGGAAGGAGT ATGATACAGA CATGGCTTTG

2701 TACACTGGAC AGGCCGGGGC TCCGCTGGCC CCACTCGCAG AGGTAGAGGA

2751 CGATGTGGAA TATTGTGGTG AAGGCGGTGC CCTACCCACC TCACAACATA

5   2801 GTGCTGGAGT TCAGGCCGGT GACCTCCCTC CAGAGACCAA GCAGCTCACT

2851 AGCCCGGATG ACCAAGGGGT TGAAATGGAA GTATTTTCTG AAGAAGATCT

2901 GCATTTAAGC ATACAGAGTC CTCGAAAGAA GTCTGACGCA GTGAGCATGC

10  2951 TCTCGGAATG CAGCACAATT GACCTGAATG ATATCTTTAG AAATTTACAG

3001 AAAACAGTTT CCCCCAAAAA GCAGCCAGAT AGATGCTTTC CCAAGGGCCT

15  3051 TAGTTGTCAC TTTCTATGCC ACAAAACAGA CAAGAGAAAG TCCCCCTGGG

3101 TCCTGTGGTG AACATTCGG AAAACCTGCT ACCAAATCGT GAAGCACAGC

3151 TGGTTTGAGA GTTTCATAAT CTTTGTTATT CTGCTGAGCA GTGGAGCGCT

20  3201 GATATTTGAA GATGTCAATC TCCCCAGCCG GCCCCAAGTT GAGAAATTAC

3251 TAAGGTGTAC CGATAATATT TTCACATTTA TTTTCCTCCT GGAAATGATC

25  3301 CTGAAGTGGG TGGCCTTTGG ATTCCGGAGG TATTTCACCA GTGCCTGGTG

3351 CTGGCTTGAT TTCCTCATTG TGGTGGTGTC TGTGCTCAGT CTCATGAATC

3401 TACCAAGCTT GAAGTCCTTC CGGACTCTGC GGGCCCTGAG ACCTCTGCGG

30  3451 GCGCTGTCCC AGTTTGAAGG AATGAAGGTT GTCGTCTACG CCCTGATCAG

3501 CGCCATACCT GCCATTCTCA ATGTCTTGCT GGTCTGCCTC ATTTTCTGGC

35  3551 TCGTATTTTG TATCTTGGGA GTAAATTTAT TTTCTGGGAA GTTTGGAAGG

3601 TGCATTAACG GGACAGACAT AAATATGTAT TTGGATTTTA CCGAAGTTCC

**SUBSTITUTE SHEET (RULE 26)**

3651 GAACCGAAGC CAATGTAACA TTAGTAATTA CTCGTGGAAG GTCCCGCAGG

3701 TCAACTTTGA CAACGTGGGG AATGCCTATC TCGCCCTGCT GCAAGTGGCA

3751 ACCTATAAGG GCTGGCTGGA AATCATGAAT GCTGCTGTCG ATTCCAGAGA

3801 GAAAGACGAG CAGCCGGACT TTGAGGCGAA CCTCTACGCG TATCTCTACT

3851 TTGTGGTTTT TATCATCTTC GGCTCCTTCT TTACCCTGAA CCTCTTTATC

3901 GGTGTTATTA TTGACAACTT CAATCAGCAG CAGAAAAAGT TAGGTGGCCA

3951 AGACATTTTT ATGACAGAAG AACAGAAGAA ATATTACAAT GCAATGAAAA

4001 AGTTAGGAAC CAAGAAACCT CAAAAGCCCA TCCCAAGGCC CCTGAACAAA

4051 TGTCAAGCCT TTGTGTTCGA CCTGGTCACA AGCCAGGTCT TTGACGTCAT

4101 CATTCTGGGT CTTATTGTCT TAAATATGAT TATCATGATG GCTGAATCTG

4151 CCGACCAGCC CAAAGATGTG AAGAAAACCT TTGATATCCT CAACATAGCC

4201 TTCGTGGTCA TCTTTACCAT AGAGTGTCTC ATCAAAGTCT TTGCTTTGAG

4251 GCAACACTAC TTCACCAATG CTGGAACTT ATTTGATTGT GTGGTCGTGG

4301 TTCTTTCTAT CATTAGTACC CTGGTTTCCC GCTTGGAGGA CAGTGACATT

4351 TCTTTCCCGC CCACGCTCTT CAGAGTCGTC CGCTTGGCTC GGATTGGTCG

4401 AATCCTCAGG CTGGTCCGGG CTGCCCGGGG AATCAGGACC CTCCTCTTTG

4451 CTTTGATGAT GTCTCTCCCC TCTCTCTTCA ACATCGGTCT GCTGCTCTTC

4501 CTGGTGATGT TCATTTACGC CATCTTTGGG ATGAGCTGGT TTTCCAAAGT

4551 GAAGAAGGGC TCCGGGATCG ACGACATCTT CAACTTCGAG ACCTTTACGG

4601 GCAGCATGCT GTGCCTCTTC CAGATAACCA CTTCGGCTGG CTGGGATACC

5    4651 CTCCTCAACC CCATGCTGGA GGCAAAGAA CACTGCAACT CCTCCTCCCA

4701 AGACAGCTGT CAGCAGCCGC AGATAGCCGT CGTCTACTTC GTCAGTTACA

4751 TCATCATCTC CTTCCTCATC GTGGTCAACA TGTACATCGC TGTGATCCTC

10   4801 GAGAACTTCA ACACAGCCAC GGAGGAGAGC GAGGACCCTC TGGGAGAGGA

4851 CGACTTTGAA ATCTTCTATG AGGTCTGGGA GAAGTTTGAC CCCGAGGCGT

15   4901 CGCAGTTCAT CCAGTATTCG GCCCTCTCTG ACTTTGCGGA CGCCCTGCCG

4951 GAGCCGTTGC GTGTGGCCAA GCCGAATAAG TTTCAGTTTC TAGTGATGGA

5001 CTTGCCCATG GTGATGGGCG ACCGCCTCCA TTGCATGGAT GTTCTCTTTG

20   5051 CTTTCACTAC CAGGGTCCTC GGGGACTCCA GCGGCTTGGA TACCATGAAA

5101 ACCATGATGG AGGAGAAGTT TATGGAGGCC AACCCTTTTA AGAAGCTCTA

25   5151 CGAGCCCATA GTCACCACCA CCAAGAGGAA GGAGGAGGAG CAAGGCGCCG

5201 CCGTCATCCA GAGGGCCTAC CGGAAACACA TGGAGAAGAT GGTCAAACTG

5251 AGGCTGAAGG ACAGGTCAAG TTCATCGCAC CAGGTGTTTT GCAATGGAGA

30   5301 CTTGTCCAGC TTGGATGTGG CCAAGGTCAA GGTTCACAAT GACTGAACCC

5351 TCATCTCCAC CCCTACCTCA CTGCCTCACA GCTTAGCCTC CAGCCTCTGG

35   5401 CGAGCAGGCG GCAGACTCAC TGAACACAGG CCGTTCGATC TGTGTTTTTG

5451 GCTGAACGAG GTGACAGGTT GGCGTCCATT TTTAAATGAC TCTTGGAAAG

5501 ATTTCATGTA GAGAGATGTT AGAAGGGACT GCAAAGGACA CCGACCATAA

5551 CGGAAGGCCT GGAGGACAGT CCAACTTACA TAAAGATGAG AAACAAGAAG

5601 GAAAGATCCC AGGAAAACTT CAGATTGTGT CTCAGTACA TTCCCCAATG

5651 TGTCTGTTCG GTGTTTTGAG TATGTGACCT GCCACATGTA GCTCTTTTTT

5701 GCATGTACGT CAAAACCCTG CAGTAAGTTA ATAGCTTGCT ACGGGTGTTC

5751 CTACCAGCAT CACAGAATTG GGTGTATGAC TCAAACCTAA AAGCATGACT

5801 CTGACTTGTC AGTCAGCACC CCGACTTTCA GACGCTCCAA TCTCTGTCCC

5851 AGGTGTCTAA CGAATAAATA GGTAAAAGAA AAAAAAAAA AAAAAAA

## SEQ.No.2

-47 GGAGCCATACGGTGCCCTGATCCTCTGTACCAGGAAGACAGGGTGAAGATGGAGGAGAGG 12
  1                        M E E R   4

13 TACTACCCGGTGATCTTCCCGGACGAGCGGAATTTCCGCCCCTTCACTTCCGACTCTCTG 72
  5 Y Y P V I F P D E R N F R P F T S D S L   24

73 GCTGCCATAAAGAAGCGGATTGCTATCCAAAAGGAGAGGAAGAAGTCCAAAGACAAGGCG 132
 25 A A I K K R I A I Q K E R K K S K D K A   44

133 GCAGCTGAGCCCCAGCCTCGGCCTCAGCTTGACCTAAAGGCCTCCAGGAAGTTACCTAAG 192
 45 A A E P Q P R P Q L D L K A S R K L P K   64

193 CTTTATGGTGACATTCCCCCTGAGCTTGTTACGAAACCTCTGGAGGACCTGGACCCCTAC 252
 65 L Y G D I P P E L V T K P L E D L D P Y   84

253 TACAAAGACCATAAGACATTCATGGTGTTGAACAAGAAAAGAACAATTTATCGCTTCAGC 312
 85 Y K D H K T F M V L N K K R T I Y R F S   104

313 GCCAAGCGGGCCTTGTTCATTCTGGGGCCTTTTAATCCCCTCAGAAGCTTAATGATTCGT 372
105 A K R A L F I L G P F N P L R S L M I R   124

373 ATCTCTGTCCATTCAGTCTTTAGCATGTTCATCATCTGCACGGTGATCATCAACTGTATG 432
125 I S V H S V F S M F I I C T V I I N C M   144

433 TTCATGGCGAATTCTATGGAGAGAAGTTTCGACAACGACATTCCCGAATACGTCTTCATT 492
145 F M A N S M E R S F D N D I P E Y V F I   164

493 GGGATTTATATTTTAGAAGCTGTGATTAAAATATTGGCAAGAGGCTTCATTGTGGATGAG 552
165 G I Y I L E A V I K I L A R G F I V D E   184

553 TTTTCCTTCCTCCGAGATCCGTGGAACTGGCTGGACTTCATTGTCATTGGAACAGCGATC 612
185 F S F L R D P W N W L D F I V I G T A I   204

613 GCAACTTGTTTTCCGGGCAGCCAAGTCAATCTTTCAGCTCTTCGTACCTTCCGAGTGTTC 672
205 A T C F P G S Q V N L S A L R T F R V F   224

673 AGAGCTCTGAAGGCGATTTCAGTTATCTCAGGTCTGAAGGTCATCGTAGGTGCCCTGCTG 732
225 R A L K A I S V I S G L K V I V G A L L   244

733 CGCTCGGTGAAGAAGCTGGTAGACGTGATGGTCCTCACTCTCTTCTGCCTCAGCATCTTT 792
245 R S V K K L V D V M V L T L F C L S I F   264

793 GCCCTGGTCGGTCAGCAGCTGTTCATGGGAATTCTGAACCAGAAGTGTATTAAGCACAAC 852
265 A L V G Q Q L F M G I L N Q K C I K H N 284

853 TGTGGCCCCAACCCTGCATCCAACAAGGATTGCTTTGAAAAGGAAAAAGATAGCGAAGAC 912
285 C G P N P A S N K D C F E K E K D S E D 304

913 TTCATAATGTGTGGTACCTGGCTCGGCAGCAGACCCTGTCCCAATGGTTCTACGTGCGAT 972
305 F I M C G T W L G S R P C P N G S T C D 324

973 AAAACCACATTGAACCCAGACAATAATTATACAAAGTTTGACAACTTTGGCTGGTCCTTT 1032
325 K T T L N P D N N Y T K F D N F G W S F 344

1033 CTCGCCATGTTCCGGGTTATGACTCAAGACTCCTGGGAGAGGCTTTACCGACAGATCCTG 1092
345 L A M F R V M T Q D S W E R L Y R Q I L 364

1093 CGGACCTCTGGGATCTACTTTGTCTTCTTCTTCGTGGTGGTCATCTTCCTGGGCTCCTTC 1152
365 R T S G I Y F V F F F V V V I F L G S F 384

1153 TACCTGCTTAACCTAACCCTGGCTGTTGTCACCATGGCTTATGAAGAACAGAACAGAAAT 1212
385 Y L L N L T L A V V T M A Y E E Q N R N 404

1213 GTAGCTGCTGAGACAGAGGCCAAGGAGAAAATGTTTCAGGAAGCCCAGCAGCTGTTAAGG 1272
405 V A A E T E A K E K M F Q E A Q Q L L R 424

1273 GAGGAGAAGGAGGCTCTGGTTGCCATGGGAATTGACAGAAGTTCCCTTAATTCCCTTCAA 1332
425 E E K E A L V A M G I D R S S L N S L Q 444

1333 GCTTCATCCTTTTCCCCGAAGAAGAGGAAGTTTTTCGGTAGTAAGACAAGAAAGTCCTTC 1392
445 A S S F S P K K R K F F G S K T R K S F 464

1393 TTTATGAGAGGGTCCAAGACGGCCCAAGCCTCAGCGTCTGATTCAGAGGACGATGCCTCT 1452
465 F M R G S K T A Q A S A S D S E D D A S 484

1453 AAAAATCCACAGCTCCTTGAGCAGACCAAACGACTGTCCCAGAACTTGCCAGTGGATCTC 1512
485 K N P Q L L E Q T K R L S Q N L P V D L 504

1513 TTTGATGAGCACGTGGACCCCCTCCACAGGCAGAGAGCGCTGAGCGCTGTCAGTATCTTA 1572
505 F D E H V D P L H R Q R A L S A V S I L 524

1573 ACCATCACCATACAGGAACAAGAAAAATTCCAGGAGCCTTGTTTCCCATGTGGGAAAAAT 1632
525 T I T I Q E Q E K F Q E P C F P C G K N 544

1633 TTGGCCTCTAAGTACCTGGTGTGGGACTGTAGCCCTCAGTGGCTGTGCATAAAGAAGGTC 1692
545 L A S K Y L V W D C S P Q W L C I K K V 564

1693 CTGCGGACCATCATGACGGATCCCTTTACTGAGCTGGCCATCACCATCTGCATCATCATC 1752

565 L R T I M T D P F T E L A I T I C I I I  584

1753 AATACCGTTTTCTTAGCCGTGGAGCACCACAACATGGATGACAACTTAAAGACCATACTG 1812
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1813 AAAATAGGAAACTGGGTTTTCACGGGAATTTTCATAGCGGAAATGTGTCTCAAGATCATC 1872
605 K I G N W V F T G I F I A E M C L K I I  624

1873 GCGCTCGACCCTTACCACTACTTCCGGCACGGCTGGAATGTTTTTGACAGCATCGTGGCC 1932
625 A L D P Y H Y F R H G W N V F D S I V A  644

1933 CTCCTGAGTCTCGCTGATGTGCTCTACAACACACTGTCTGATAACAATAGGTCTTTCTTG 1992
645 L L S L A D V L Y N T L S D N N R S F L  664

1993 GCTTCCCTCAGAGTGCTGAGGGTCTTCAAGTTAGCCAAATCCTGGCCCACGTTAAACACT 2052
665 A S L R V L R V F K L A K S W P T L N T  684

2053 CTCATTAAGATCATCGGCCACTCCGTGGGCGCGCTTGGAAACCTGACTGTGGTCCTGACT 2112
685 L I K I I G H S V G A L G N L T V V L T  704

2113 ATCGTGGTCTTCATCTTTTCTGTGGTGGGCATGCGGCTCTTCGGCACCAAGTTTAACAAG 2172
705 I V V F I F S V V G M R L F G T K F N K  724

2173 ACCGCCTACGCCACCCAGGAGCGGCCCAGGCGGCGCTGGCACATGGATAATTTCTACCAC 2232
725 T A Y A T Q E R P R R R W H M D N F Y H  744

2233 TCCTTCCTGGTGGTGTTCCGCATCCTCTGTGGGGAATGGATCGAGAACATGTGGGGCTGC 2292
745 S F L V V F R I L C G E W I E N M W G C  764

2293 ATGCAGGATATGGACGGCTCCCCGTTGTGCATCATTGTCTTTGTCCTGATAATGGTGATC 2352
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2353 GGGAAGCTTGTGGTGCTTAACCTCTTCATTGCCTTGCTGCTCAATTCCTTCAGCAATGAG 2412
785 G K L V V L N L F I A L L L N S F S N E  804

2413 GAGAAGGATGGGAGCCTGGAAGGAGAGACCAGGAAAACCAAAGTGCAGCTAGCCCTGGAT 2472
805 E K D G S L E G E T R K T K V Q L A L D  824

2473 CGGTTCCGCCGGGCCTTCTCCTTCATGCTGCACGCTCTTCAGAGTTTTTGTTGCAAGAAA 2532
825 R F R R A F S F M L H A L Q S F C C K K  844

2533 TGCAGGAGGAAAAACTCGCCAAAGCCAAAAGAGACAACAGAAAGCTTTGCTGGTGAGAAT 2592
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2593 AAAGACTCAATCCTCCCGGATGCGAGGCCCTGGAAGGAGTATGATACAGACATGGCTTTG 2652
865 K D S I L P D A R P W K E Y D T D M A L  884

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885 Y T G Q A G A P L A P L A E V E D D V E   904

2713 TATTGTGGTGAAGGCGGTGCCCTACCCACCTCACAACATAGTGCTGGAGTTCAGGCCGGT 2772
905 Y C G E G G A L P T S Q H S A G V Q A G   924

2773 GACCTCCCTCCAGAGACCAAGCAGCTCACTAGCCCGGATGACCAAGGGGTTGAAATGGAA 2832
925 D L P P E T K Q L T S P D D Q G V E M E   944

2833 GTATTTTCTGAAGAAGATCTGCATTTAAGCATACAGAGTCCTCGAAAGAAGTCTGACGCA 2892
945 V F S E E D L H L S I Q S P R K K S D A   964

2893 GTGAGCATGCTCTCGGAATGCAGCACAATTGACCTGAATGATATCTTTAGAAATTTACAG 2952
965 V S M L S E C S T I D L N D I F R N L Q   984

2953 AAAACAGTTTCCCCCAAAAAGCAGCCAGATAGATGCTTTCCCAAGGGCCTTAGTTGTCAC 3012
985 K T V S P K K Q P D R C F P K G L S C H   1004

3013 TTTCTATGCCACAAAACAGACAAGAGAAAGTCCCCCTGGGTCCTGTGGTGGAACATTCGG 3072
1005 F L C H K T D K R K S P W V L W W N I R   1024

3073 AAAACCTGCTACCAAATCGTGAAGCACAGCTGGTTTGAGAGTTTCATAATCTTTGTTATT 3132
1025 K T C Y Q I V K H S W F E S F I I F V I   1044

3133 CTGCTGAGCAGTGGAGCGCTGATATTTGAAGATGTCAATCTCCCCAGCCGGCCCCAAGTT 3192
1045 L L S S G A L I F E D V N L P S R P Q V   1064

3193 GAGAAATTACTAAGGTGTACCGATAATATTTTCACATTTATTTTCCTCCTGGAAATGATC 3252
1065 E K L L R C T D N I F T F I F L L E M I   1084

3253 CTGAAGTGGGTGGCCTTTGGATTCCGGAGGTATTTCACCAGTGCCTGGTGCTGGCTTGAT 3312
1085 L K W V A F G F R R Y F T S A W C W L D   1104

3313 TTCCTCATTGTGGTGGTGTCTGTGCTCAGTCTCATGAATCTACCAAGCTTGAAGTCCTTC 3372
1105 F L I V V V S V L S L M N L P S L K S F   1124

3373 CGGACTCTGCGGGCCCTGAGACCTCTGCGGGCGCTGTCCCAGTTTGAAGGAATGAAGGTT 3432
1125 R T L R A L R P L R A L S Q F E G M K V   1144

3433 GTCGTCTACGCCCTGATCAGCGCCATACCTGCCATTCTCAATGTCTTGCTGGTCTGCCTC 3492
1145 V V Y A L I S A I P A I L N V L L V C L   1164

3493 ATTTTCTGGCTCGTATTTTGTATCTTGGGAGTAAATTTATTTTCTGGGAAGTTTGGAAGG 3552
1165 I F W L V F C I L G V N L F S G K F G R   1184

3553 TGCATTAACGGGACAGACATAAATATGTATTTGGATTTTACCGAAGTTCCGAACCGAAGC 3612
1185 C I N G T D I N M Y L D F T E V P N R S   1204

12

3613 CAATGTAACATTAGTAATTACTCGTGGAAGGTCCCGCAGGTCAACTTTGACAACGTGGGG 3672
1205 Q C N I S N Y S W K V P Q V N F D N V G 1224


5

3673 AATGCCTATCTCGCCCTGCTGCAAGTGGCAACCTATAAGGGCTGGCTGGAAATCATGAAT 3732
1225 N A Y L A L L Q V A T Y K G W L E I M N 1244


3733 GCTGCTGTCGATTCCAGAGAGAAAGACGAGCAGCCGGACTTTGAGGCGAACCTCTACGCG 3792
1245 A A V D S R E K D E Q P D F E A N L Y A 1264

10

3793 TATCTCTACTTTGTGGTTTTTATCATCTTCGGCTCCTTCTTTACCCTGAACCTCTTTATC 3852
1265 Y L Y F V V F I I F G S F F T L N L F I 1284


3853 GGTGTTATTATTGACAACTTCAATCAGCAGCAGAAAAAGTTAGGTGGCCAAGACATTTTT 3912
15 1285 G V I I D N F N Q Q Q K K L G G Q D I F 1304


3913 ATGACAGAAGAACAGAAGAAATATTACAATGCAATGAAAAAGTTAGGAACCAAGAAACCT 3972
1305 M T E E Q K K Y Y N A M K K L G T K K P 1324


20

3973 CAAAAGCCCATCCCAAGGCCCCTGAACAAATGTCAAGCCTTTGTGTTCGACCTGGTCACA 4032
1325 Q K P I P R P L N K C Q A F V F D L V T 1344


4033 AGCCAGGTCTTTGACGTCATCATTCTGGGTCTTATTGTCTTAAATATGATTATCATGATG 4092
1345 S Q V F D V I I L G L I V L N M I I M M 1364

25

4093 GCTGAATCTGCCGACCAGCCCAAAGATGTGAAGAAAACCTTTGATATCCTCAACATAGCC 4152
1365 A E S A D Q P K D V K K T F D I L N I A 1384


4153 TTCGTGGTCATCTTTACCATAGAGTGTCTCATCAAAGTCTTTGCTTTGAGGCAACACTAC 4212
30 1385 F V V I F T I E C L I K V F A L R Q H Y 1404


4213 TTCACCAATGGCTGGAACTTATTTGATTGTGTGGTCGTGGTTCTTTCTATCATTAGTACC 4272
1405 F T N G W N L F D C V V V V L S I I S T 1424


35

4273 CTGGTTTCCCGCTTGGAGGACAGTGACATTTCTTTCCCGCCCACGCTCTTCAGAGTCGTC 4332
1425 L V S R L E D S D I S F P P T L F R V V 1444


4333 CGCTTGGCTCGGATTGGTCGAATCCTCAGGCTGGTCCGGGCTGCCCGGGGAATCAGGACC 4392
1445 R L A R I G R I L R L V R A A R G I R T 1464

40

4393 CTCCTCTTTGCTTTGATGATGTCTCTCCCCTCTCTCTTCAACATCGGTCTGCTGCTCTTC 4452
1465 L L F A L M M S L P S L F N I G L L L F 1484


4453 CTGGTGATGTTCATTTACGCCATCTTTGGGATGAGCTGGTTTTCCAAAGTGAAGAAGGGC 4512
45 1485 L V M F I Y A I F G M S W F S K V K K G 1504


4513 TCCGGGATCGACGACATCTTCAACTTCGAGACCTTTACGGGCAGCATGCTGTGCCTCTTC 4572


**SUBSTITUTE SHEET (RULE 26)**

1505 S G I D D I F N F E T F T G S M L C L F 1524

4573 CAGATAACCACTTCGGCTGGCTGGGATACCCTCCTCAACCCCATGCTGGAGGCAAAAGAA 4632
1525 Q I T T S A G W D T L L N P M L E A K E 1544

4633 CACTGCAACTCCTCCTCCCAAGACAGCTGTCAGCAGCCGCAGATAGCCGTCGTCTACTTC 4692
1545 H C N S S S Q D S C Q Q P Q I A V V Y F 1564

4693 GTCAGTTACATCATCATCTCCTTCCTCATCGTGGTCAACATGTACATCGCTGTGATCCTC 4752
1565 V S Y I I I S F L I V V N M Y I A V I L 1584

4753 GAGAACTTCAACACAGCCACGGAGGAGAGCGAGGACCCTCTGGGAGAGGACGACTTTGAA 4812
1585 E N F N T A T E E S E D P L G E D D F E 1604

4813 ATCTTCTATGAGGTCTGGGAGAAGTTTGACCCCGAGGCGTCGCAGTTCATCCAGTATTCG 4872
1605 I F Y E V W E K F D P E A S Q F I Q Y S 1624

4873 GCCCTCTCTGACTTTGCGGACGCCCTGCCGGAGCCGTTGCGTGTGGCCAAGCCGAATAAG 4932
1625 A L S D F A D A L P E P L R V A K P N K 1644

4933 TTTCAGTTTCTAGTGATGGACTTGCCCATGGTGATGGGCGACCGCCTCCATTGCATGGAT 4992
1645 F Q F L V M D L P M V M G D R L H C M D 1664

4993 GTTCTCTTTGCTTTCACTACCAGGGTCCTCGGGGACTCCAGCGGCTTGGATACCATGAAA 5052
1665 V L F A F T T R V L G D S S G L D T M K 1684

5053 ACCATGATGGAGGAGAAGTTTATGGAGGCCAACCCTTTTAAGAAGCTCTACGAGCCCATA 5112
1685 T M M E E K F M E A N P F K K L Y E P I 1704

5113 GTCACCACCACCAAGAGGAAGGAGGAGGAGCAAGGCGCCGCCGTCATCCAGAGGGCCTAC 5172
1705 V T T T K R K E E E Q G A A V I Q R A Y 1724

5173 CGGAAACACATGGAGAAGATGGTCAAACTGAGGCTGAAGGACAGGTCAAGTTCATCGCAC 5232
1725 R K H M E K M V K L R L K D R S S S S H 1744

5233 CAGGTGTTTTGCAATGGAGACTTGTCCAGCTTGGATGTGGCCAAGGTCAAGGTTCACAAT 5292
1745 Q V F C N G D L S S L D V A K V K V H N 1764

5293 GACTGAACCCTCATCTCCACCCCTACCTCACTGCCTCACAGCTTAGCCTCCAGCCTCTGG 5352
1765 D • 1766

5353 CGAGCAGGCGGCAGACTCACTGAACACAGGCCGTTCGATCTGTGTTTTTGGCTGAACGAG 5412

5413 GTGACAGGTTGGCGTCCATTTTTAAATGACTCTTGGAAAGATTTCATGTAGAGAGATGTT 5472

5473 AGAAGGGACTGCAAAGGACACCGACCATAACGGAAGGCCTGGAGGACAGTCCAACTTACA 5532

14

5533 TAAAGATGAGAAACAAGAAGGAAAGATCCCAGGAAAACTTCAGATTGTGTTCTCAGTACA 5592

5593 TTCCCCAATGTGTCTGTTCGGTGTTTTGAGTATGTGACCTGCCACATGTAGCTCTTTTTT 5652

5   5653 GCATGTACGTCAAAACCCTGCAGTAAGTTAATAGCTTGCTACGGGTGTTCCTACCAGCAT 5712

5713 CACAGAATTGGGTGTATGACTCAAACCTAAAAGCATGACTCTGACTTGTCAGTCAGCACC 5772

5773 CCGACTTTCAGACGCTCCAATCTCTGTCCCAGGTGTCTAACGAATAAATAGGTAAAAGAA 5832

10

5833 AAAAAAAAAAAAAAAAA 5849

## Human SNS₂ₐ sequences

**SEQ.I.D.NO:3**

ATCCTAGGGCAGGCTGTTTTATTCCCGCCTCCTGAGGCCTTTCTGAGGATCTGTGGCTTG
TCTCTGTCCTGAGGGTGAAGATGGATGACAGATGCTACCCAGTAATCTTTCCAGATGAGC
GGAATTTCCGCCCCTTCACTTCCGACTCTCTGGCTGCAATTGAGAAGCGGATTGCCATCC
AAAAGGAGAAAAAGAAGTCTAAAGACCAGACAGGAGAAGTACCCCAGCCTCAACCTCAG
C
TTGACCTAAAGGCCTCCAGGAAGTTGCCCAACTCTATGGCGACAATCCTCGGAGGCTTT

**SEQ.I.D.NO.4**

CGCTCTGTGAAGAAGCTGGTCAACGTGATTATCCTCACCTTCTTTTGCCTCAGCATCTTT
GCCCTGGTAGGTCAGCAGCTCTTCATGGGAAGTCTGAACCTGAAATGCATCTCGAGGGAC
TGTAAAAATATCAGTAACCC

**SEQ.I.D.NO.5**

TAAAAATATCAGTAACCCGGAAGCTTATGACCATTGCTTTGAAAAGAAAGAAAATTCACC
TGAATTCAAAATGTGTGGCATCTGGATGGGTAACAGTGCCTGTTCCATACAATATGAATG
TAAGCACACCAAAATTAATCCTGACTATAATTATACGAATTTTGACAACTTTGGCTGGTC
TTTTCTTGCCATGTTCCGGCTGATGACCCAAGATTCCTGGGAGAAGCTTTAT

**SEQ.I.D.NO.6**

ACTACTGGGTCTACTCAGTCTTCTTCTTCATTGTGGTCATTTTCCTGGGGCTCCCTTCTA
CCTGATTAACTTAAACCCTGGCTGTTGTTACCATGGGCATATGAGGAGCCGAACAAGAAT
GTAGCTGCAGAGATAGAGGCCCAGGAAAAGATGTTCAGGAAGCCCAGCAGCTGGTTAAA
G

**SEQ.I.D.NO.7**

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TTGTCAGCATCCTCACCATCACCATGAAGGGTAAGTTCCACATCCCAATCCAAGGGAAAG
TCTACTTCAGTGATGTCCTTCCATTCTTCTTCTTCCCAATCCCCTAGAAGCCCTCTGCAA

**SEQ.I.D.NO.8**

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AAGAAAAATCACAAGAGCCTTGTCTCCCTTGTGGAGAAAACCTGGCATCCAAGTACCTCG
TGTGGAACTGTTGCCCCCAGTGGCTGTGCGTAAAGAAGGTCCTGAGAACCGTCATGACGG
TCCCGTTTACTGAGCTGGACATCACGATCTGCATCATCATCAACACAGACTTCTTGGACA
TGGAGCATCACAAGATGTAAGGCAACGTATTGGAGACGATGTTGAATATAGGGCAGTAG

**SEQ.I.D.No.9**

GCAGATGGAGTTCGCTTAACTGGCTTTTCTCCGTTTTCGTTCGTCGCTTTTTCTACAGCT
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ACTCTCGTCGGAGCCCTTGGAAGCCTGACTGTGGTCCTGGTCATTGTGATCTTTATTTTC
TCAGTAGTTGGCATGCAGCTTTTTGGCCGTAGCTTCAATTCCCAAAAGAGTCCAAAACTC
TGTAACCCGACAGGCCCGACAGTCTCATGTTTACGGCACTGGCACATGGGGGATTTCTGG
CACTCCTTCCTAGTGGTATCGCGCATCCTCTTGCG

**SEQ.I.D.NO.10**

CTCTGTACCAAAGACCCTGGGCGTCAGGCATGATTGGACTTGGTTGGCACCACTTGCGGA
GGAGGAAGATGACGTTGAATTTTCTGGTGAAGATAATGCACAGCGCATCACACAACCTGA
GCCTGAACAACAGGTATGAAGGTTCACACATAGACTTAAAGGTCATACAAAGCTGGAGTT
ATCACAGGGCACTGGTAGCCTACCCTTTTCTAGGCACTATGCAAGGATAATAAGGATTCT

CGTACGCACGGGTACGATTCG

SEQ.I.D.NO.11

CAGACAATGAGAAACTCCGTACTACTATGGTGAAAGAAGGTCTTAGTAAAAGGCACCCCC
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CATTGATCTTCAGGATGGCTTTGGATGGTTACCTGAGATGGTTCCCAAAGAAAAATTTCC
AGCGATTTTTCGTACCAACGGTTACGCTTCGAAGG

SEQ.I.D.NO.12

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GAATGAAGGTACATTCTGCAGAAGAATGGGTAGAAGTTCAGTTAACAGAGAAAGGTGGA
A
AGACCAACAGTTCTTTTTGGGCTGAGATTTCCTTAAATTGCCAAGCTTTTCCTGGGTTAC
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TACCCTAAAAGCTTCTGTGACAGCCAAGATGAGCTGTAGCGAAGGAATTC

SEQ.I.D.NO.13

GGTGCATCCCTACCCCATCTGTTATGGTTTTCCTTTGCTTTTGTTTTCCATAAGGTGGT
GGTCAATGCTCTCATAGGTGCCATACCTCCCATTCCTGAATGTTTTGCTTGTCTGCCTCA
TTTTCTGGCTCGTATTTTGTATTCTGGGAGTATACTTCCTTTTCCTGGAAAATTTGGGAA
ATGCATTCAATGGAACAGACTTTTAGGAATTTCCAGCGATTCCT

SEQ.I.D.NO.14

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ATCGTTTATGCAGCTGTTGATTCCACAGAGGTGAGTCAGTGTTCTACCATGTTCGGCAGT
GTTATGGTCAAGTCAGAGATATCATGACTACATGGACAGTCCAGAACTGGCGTCATAGTT
CCAGCAGCTGGGGTTCTCTGCCTTGTTTCCTTTGGAACAAAACACTATGAGATACCACTG
CCTA

SEQ.I.D.NO.15

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AGGCTCCCAACAGGGGCTATGGCTGTTAGGAAGAGGCTATGTAGTCAATGTTGCTGCTAA
GAAACACCTTGGTCTTCTAGATAAGGTAGTTAGAATGCTTATATTTTTCTCCAGTAATTG
TTTTTTTCTCTTATTAAAAAAATTTCTAACAGAAAGAACAACAGCCAGAGTTTGAGAGCA
ATTCACTCGGTTACATTTCTTCGTAGTCTTTATCATCTTTGGCTCATTCTTCACTCTGAA
TCTCTTCATTGGCGTTATCATTGACAACTTCAACCAACAGCAGAAAAAGATAAGTATCTG
GGTTGTCTTGATTTGGTAATTGTATCTCTGTCCTCCAAAGAAGGAATCC

SEQ.I.D.NO.16

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CCATGGAATCCATCCTTGACCATCTCCAACTGGGTCTTTGTGGTCATCTTTACGTTAGAA
TGTCTCATCAAAATCTTTGCTTTGAGGCAATACTACTTCACCAATGGCTGGAATTTATTT
GACTGTGTGGTCGTGCTTCTTTCCATTGTTAGTAAGTAAAATCAGCAGTCAGAGGGACTT
TAAGAACCAGAAGTAAGTTTGTAAATCTTATCATTTTTTGAAGTTTGTTCAAACTATCCA
CAAAGCAGAAAACTGGGCCAAGTGTACTTTCTGAAAGAATAGACAGGGGTACTAATGCCA
TTCTCTACTGGGAAGTTGCTAGGAGATAGGAGGCGGTAAATTTCTGGTTCCCCTTAACTC

ACTACACAACTGAAATAGAGTTCAATAATCATGCAGCTAATGTATTCAATGGAAATAGAC
AAAATTAAAATGACTCAGAAGTTTTTGTGGTGGTAGAAAAATTTC

5

**SEQ.I.D.NO:17**

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TGCAATGGAGACTTGTCTAGCTTTGGGGTGGCCAAGGGCAAGGTCCACTGTGACTGAGCC
10  CTCACCTCCACGCCTACCTCATAGCTTCACAGCCTTGCCTTCAGCCTCTGAGCTCCAGGG
GTCAGCAGCTTAGTGTATCAACAGGGAGTGGATTCACCAAATT